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COVID 19 IN PREGNANT WOMEN - A RETROSPECTIVE COHORT STUDY

Gebe Kadınlarda Covid 19 - Retrospektif Kohort Çalışması

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ABSTRACT

Aim: *Our aim is to summarize the clinical signs, symptoms, treatment andprognosis of pregnant women with COVID-19 comparing with non pregnant women with COVID-19 at similar age interval.*

Method: *A retrospective study was conducted by reviewing the medical records of all symptomatic pregnant women infected with COVID-19 between March 15 and May 31, 2020. Pregnant women (n=21) who applied to tertiary hospital during the same time period and with covid-19 diagnosis formed our working group, and control group (n=90) consisted of women who were symptomatic of reproductive age and not pregnant. Seven pregnant women and fifteen non pregnant women were excluded due to being asymptomathic and SARS- CoV-2 positive. COVID-19 infection was diagnosed with computed tomography (CT) scans. For laboratory confirmation with PCR, patients were asked to give nasopharyngeal swab samples and tested for SARS-CoV-2 with the blood-based immunoassay kit launchedprovided by Bio-Rad Laboratories.*

Results: *Between March 15 to May 31, 2020, there were 21 pregnant women and 90 non-pregnant women who have confirmed infection for COVID-19. Seven pregnant women and 15 non-pregnant women were SARS-CoV-2 positive and asymptomatic; they are not included in the study. Fourteen pregnant women and 75 non-pregnant women are included in the study. There were no statistically significant difference between groups concerning the incidence of the symptoms (p> 0.05). Early stage is characterized by the ground glass opacities (GGO), which is common in Covid-19 disease, located in the peripheral and subpleural area. In what concerns the severity of the clinical course; the need for hospitalization, the length of hospital stay, the need for mechanical ventilation were statistically significantly higher in pregnant group. All the two groups were prescribed Hydroxychloroquine and antivirals at a similar rate but the use of antibiotics and low molecular weight heparin was statistically significantly higher in pregnant group.*

Conclusion and Suggestions*: We found that COVID-19 infection hassimilar clinical characteristics and a similar rate of pneumonia in pregnant women. But more studies are needed in the field to define a definitive outcome.*

Key words: *Coronavirus; Covid-19; SARS-CoV-2; Obstetric management; Pregnancy; Fever.*

ÖZET

Amaç: *Amacımız, benzer yaş aralığında COVID-19 enfeksiyonu olan gebe olmayan kadınlarla, COVID-19 enfeksiyonu bulunan gebe kadınların klinik belirti, semptom, tedavi ve prognozunu özetlemektir.*

Yöntem: *Bu çalışma 15 Mart - 31 Mayıs 2020 tarihleri arasında COVID-19 ile enfekte olantüm semptomatik gebe kadınların tıbbi kayıtlarının geriye dönük inceleme yapıldı. Aynı zaman aralığında ve COVID-19 tanısı ile üçüncü basamak bir hastaneye başvuran gebe kadınlar çalışma grubunu (n=21), üreme çağındaki semptomatik, gebe olmayan kadınlar (n=90) kontrol grubuna dahil edilmiştir. Yedi gebe kadın ve onbeş gebe olmayan kadın SARS-CoV-2 pozitif ve asemptomatik olması sebebiyle çalışma dışı bırakılmış ve 14 gebe ve 75 gebe olmayan kadın ile tamamlanmıştır. COVID-19 hastalığının teşhisi, bilgisayarlı tomografi (BT) taramalarına dayandırılmıştır. PCR ile laboratuvar onayı için, nazofaringealsüruntü örnekleri toplanmış olup Bio-Rad Laboratories tarafından sağlanan kan bazlı immünolojik test kiti ile SARS-CoV-2 için test edilmiştir.*

Bulgular: *Semptomların görülme sıklığı açısından iki grup arasında istatistiksel olarak anlamlı bir fark bulunmadı (p>0.05). Erken evre, Covid-19 hastalığında sık görülen, periferik ve subplevral bölgede yer alan buzlu cam opasiteleri (GGO) ile karakterizedir. Klinik seyrin ciddiyeti ile ilgili olarak; gebe grubunda hastanede yatış ihtiyacı, hastanede kalış süresi, mekanik ventilasyon ihtiyacı istatistiksel olarak anlamlı derecede yüksekti. Her iki gruba da benzer oranda Hidroksiklorokin ve antiviral ilaçlar reçete edildi, ancak antibiyotik ve düşük molekül ağırlıklı heparin kullanımı gebe grupta istatistiksel olarak anlamlı olarak daha yüksekti.*

Sonuçlar ve Öneriler: *COVID-19 enfeksiyonunun gebe olan ve olmayan kadınlarda benzer klinik özelliklere sahip olduğunu ve gebe kadınlarda benzer pnömoni oranına sahip olduğunu gözlemledik. Ancak kesin bir sonuca varmak için ileride yapılacak araştırmalara ihtiyaç vardır*

Anahtar kelimeler: *Koronavirüs; COVID-19; SARS-CoV-2; Obstetrik tedavi; Gebelik, Ateş.*

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1. INTRODUCTION

Coronavirus outbreak (COVID-19) was declared as pandemic by World HealthOrganization (WHO) in March 2020, afterwards it has been spread widely all over the world causing serious mortality and morbidity (Baron SA et al, 2020). With its sustained spread across countries, we will probably see many women in reproductive years, pregnant or non pregnant, with COVID-19 infection. (Chen H et al, 2020). Pregnancy is accepted as a risk factor during infectious disease, especially during pandemics (Jameieson DJ et al, 2009, Sarah K et al, 2020). Physiological changes in cardiorespiratory and immune system during pregnancy makes both mother and baby vulnerable for complications of infections (Elshafeey F et al, 2020, Wong SF et al, 2004).

A recent report on pregnancy and perinatal outcomes of the COVID-19 disease stated that the most common symptoms were fever and cough (Dehan L et al, 2020). In laboratory examinations, the most common finding was lymphocyte count reduction (Dehan L et al, 2020). They reported that most of the patients had cesarean delivery and good fetal outcome. Also no aggrevation and relapse of the pneumonia occured due to the childbirth or pregnancy. However, the severity of COVID-19 during pregnancy and whether the course differs than non pregnant women are unclear (Liu D et al, 2020).

Our aim was to summerize the clinical signs, symptoms, treatment and prognosis of the pregnant women who has COVID-19 compairng with non-pregnant women does not have COVID-19 at similar age interval.

2. MATERIALS AND METHODS

A retrospective cohort study was conducted in tertiary center, in a capital city, the first pandemic hospital in Turkey. Data was collected from the hospital records after the local ethical approval was received (2020/514/174/9). Medical records of all the symptomatic pregnant women infected with COVID-19 were reviewed from March 15 to May 31, 2020. The control group consists of symptomatic, non-pregnant women at reproductive age, who admitted to our hospital within the same time interval and had the diagnosis of COVID-19. The inclusion criteria to the control group are being diagnosed either with thorax CT and/or PCR testing, having symptoms of the disease, being aged between 18-40 years old. The exclusion criteria for the groups are only being asymptomatic; asymptomatic persons who had quantitative RT-PCR (qRT-PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the indication of having a SARS-CoV-2 positive close member in the family are not included.

The diagnosis of COVID-19 disease is based on computed tomography (CT) scans. When specific signs are found (ground glass opacity and consolidation) the patient is diagnosed to have the disease. For laboratory confirmation with PCR, nasopharyngeal swab samples were collected and tested for SARS-CoV-2 with the blood-based immunoassay kit launched provided by Bio-Rad Laboratories.

2.1. Statistical Analysis

Patients were grouped into two as pregnant and non-pregant women, and medical records, laboratory tests and chest CT imaging of the patients were retrospectively reviewed. Data were represented as mean ± standard deviation, percentages, and frequency of variables. Shapiro-Wilk and Levene tests were used to analyze the normality and homogeneity of variances. Groups were compared with the independent Samples t- test (Student's t-test) when prerequisites were met, otherwise if prerequisites were not met Mann-Whitney U test was used. $P<0.05$ was considered statistically significant.

3. RESULTS

A total of 89 patients were included for the study. The age of the pregnant patients were ranged between 20 to 46 years (mean 29.64±6.12) and the non-pregnant women, 18 to 35 years old (mean 26.3±4.99); the difference wasstatistically significant. The mean gestational age of the patients was 27.35±10.70 (6-39) weeks. None of the patients had concominant illness. Demographic data are presented in Table 1.

Table 1. Demographic data of the patients

	Pregnant women (n:14)	Non-pregnant women (n:75)	p value
Age	29.64±6.12 (20-46)	26.3±4.99 (18-35)	0.029
Gestational age*	27.35±10.70 (6-39)		
Comorbidities (n)			
Hypertension	0	1	
Diabetes	0	2	
CV disease**	0	1	

*gestational age at the diagnosis **cardiovascular disease

Table 2. Clinical characteristics of the patients

	Pregnant women (n:14)	Non-pregnant women (n:75)		p value
	n (%)	n (%)		
Signs and symptoms				
Fever	4 (28.6%)	14	(18.7%)	0.47
Cough	10 (71.4%)	55	(73.3%)	1
Dyspnea	8 (57.1%)	24 (32%)		0.072
Diarrhea	0	4	(5.3%)	0.377
Myalgia	5 (35.7%)	31	(41.3%)	0.694
Chest pain	4 (28.6%)	26	(34.7%)	0.765

* Chi-Square Test

The most common symptoms were cough (71.42%), dyspnea (57.14%) and myalgia (35.71%) in pregnant women; cough (73.33%), myalgia (41.33%), chest pain (34.66%) and dyspnea (32%) in non-pregnant women. There was no statistically significant difference between the two groups concerning the incidence of the symptoms ($p > 0.05$) (Table 2). Four pregnant patients (4/14; 28.57%) and 21 non pregnant patients (21/75, 28%) had a chest CT scan. All the patients showed typical findings of chest CT images (ground glass opacity and consolidation). Covid-19 was found to be related to evident lesions in CT scan. Patients are divided according to the CT scan findings into three groups as early stage, progressing stage and severe stage. Early stage is characterized by the ground glass opacities (GGO), which is common in Covid-19 disease, located in the peripheral and subpleural area. The ground glass opacity (GGO) is described as an irregular shaped shadow image that reduces the density of the lung tissue. Progressive stage is characterized with more intensive and inflammatory areas and centrally locatedconsolidations which contains air bronchograms. Severe stage is distinguished with bilateral and diffuse intensely consolidated areas in both lungs, acquiring a marble-like appearance.

Table 3. Severity of the clinical course.

	Pregnant women (n:14)	Non-pregnant women (n:75)	Test
	n(%)	n(%)	p value
Need for hospitalization	10 (71.4%)	13 (17.3%)	**0,000**
Pneumonia	4 (30.8%)	14(18.7%)	0,318
Admission to ICU	1 (7%)	0	**0,318**
Need for mec. vent.	2 (9.4%)	0	**0,001**
	Mean±SD	Mean±SD	
Length of hospitalization (n days)	5.90±2.02	1.04±2.52	**0,000**

***** Chi-Square Test

In what concerns the severity of the clinical course; the need for hospitalization, the length of hospital stay, the need for mechanical ventilation were statistically significantly higher in pregnant group ($p<0.05$) (Table 3). One pregnant women developed severe COVID-19 pneumonia and needed intensive care unit and mechanical ventilation.

Table 4. Medications used for the treatment of the groups

	Pregnant women (n:14)	Non-pregnant women (n:75)		Test
	n (%)	n (%)		p value
Hydroxychloroquine	14 (100%)	65	(86.7%)	0.345
Antiviral agent	2 (15.4%)	17(22.7%)		0.726
Antibiotics	5 (38.5%)	9 (12.9%)		**0.039**
LMWH[a]	7 (50%)	7	(9.3%)	**0.001**

[a] Low molecular weight heparin *Chi-Square Test

None of the non-pregnant women developed severe disease. No death occurred. The group of pregnant women consisted of all singletons. The mean gestational age at the time of diagnosis was 27 (min:6, max:39). The course of pregnancy included birth in 9 (64.29%), ongoing pregnancy 5 (35.71%) women. Among the 9 women who gave birth, 4 (44%) were delivered by cesarean section and 5 (55%) had a vaginal birth. The indications for cesarean section were fetal distress (n:) and history of cesarean section (n:). Only one newborn had a birthweight lower than 2500 g (2470 gr), the others' birthweights were below 2500 gr. All for births had a 1-min and 5-min Apgar score of 8–9. All the two groups were prescribed Hydroxychloroquine and antivirals at a similar rate but the use of antibiotics and low molecular weight heparin was statistically significantly higher in pregnantgroup ($p<0.05$) (Table 4).

4. DISCUSSION

In general, pregnant women are known to be disproportionately affected by respiratory illnesses (Dashraath P et al, 2019). To date, hundreds of pregnant women infected with COVID-19 are reported in the literature (Dotter-Katz et al, 2020). However, the severity of this infection during pregnancy is unclear. In this report, we investigated whether the clinical presentation, disease severity and course differ between pregnant and non pregnant women during reproductive years.We found that the need for hospitalization was more common and the length of hospital stay was longer in pregnant women but the risk of developing pneumonia and the need for admission to ICU was not different between the groups. As limited data were available in the beginning of the outbreak, we hospitalized every pregnant woman with laboratory confirmed COVID-19 infection. This made our statistics about hospitalization and length of hospital stay statistically significantly worse for pregnant women group.

Concerning the incidence of pneumonia, it was similar between the two groups. No non-pregnant women in the reproductive age group developed severe infection, but 2 pregnant women needed mechanical ventilation (2/14, 14.29%) and one needed admission to ICU (1/14, 7.14%). Even though the difference is statistically significant, the number of patients having severe disease are so few to state that COVID-19 has a worse clinical course in pregnancy. The data in the literature shows that COVID-19 wasfoundto be not related to worse outcomes in pregnant women than in the general population (Sarah & Brenna, 2020). No drug is currently approved to treat COVID-19, andpresently, there is no effective coronavirus drug. Only, remdesivir, an investigational antiviral drug, is recommended in patients with severe COVID-19 (National Institute of Health 2020). Drugs used in Covid 19 treatment, hydroxycholoquine, oseltamivir, ceftriaxone, azithromycin, teicoplanin, low molecul weight heparin and favipiravir. In recent studies, hydroxycholoquine was found to prevent viral entry by blocking Covid-19 and ACE2 receptor binding (Kaplan YC, 2016). It is recommended as 400 mg 2 times a day orally on the first day, and 200 mg 2 times a day for the next 4 days (Karunajeewa et al., 2010; Sanders et al, 2020). Oseltamivir was used emprically, but studies showed that it does not have in vitro activity against Covid-19 (Dembinski et al,2010). Ceftriaxone is recommended to use antibiotic therapy only in the presence of evidence of secondary bacterial infection (Breslin et al.,2020). In a clinial study, the combination of hydroxychloroquine and azithromycin was found to reduce viral load in covid-19 patients (Sanders et al, 2020; Gao J et al, 2020). Teicoplanin was shown to shown to inhibit cellular penetration of Covid-19 in vitro (Baron et al,2020). They stated that teicoplanin is a promising drug for treatment of Covid-19 disease. Ranucci et al. demonstrated the potential role of micro / macro aggregate formation in the pulmonary vasculature in the ARDS pattern in Covid-19 patients, so low molecular heparin is used to prevent thromboembolic events in patients (Ranucci et al.,2020). Favipiravir inhibits viral replication by stopping RNA polymerase (Breslin et al.,2020). Also lopinovir and ritonavir, used in HIV treatment, was ordered for patients with wide spread lung involvement due to Covid infection during pregnancy. After birth, lopinavir was switched to favipiravir (Bhatnagar et al.,2020).

Clinical experience supporting the use of favipiravir for Covid-19 is limited. However in prospective, randomized, multicenter study, favipiravir was found to be superior to Arbidol treatment in severe and moderate stage patients (Breslin et al.,2020).

The gold standart diagnostic method seems to be a real-time reverse transciptase polymerase chain reaction (RT-PCR) assay from respiratory tract from the patients whose prediagnosis is Covid-19. However, computed tomography (CT) scan of the chest can not replace molecular confirmation of the disease, but has a high sensitivity and specificity in the diagnosis of COVID-19 infection. Meanwhile, concerns regarding the teratogenic effects of ionizing radiation on the fetus should always be kept in mind.

4.1. Limitations of the study

Our study has many limitations. The control group consists of non pregnant women of reproductive age. A similar study with pregnant women without COVID-19 infection as control group would give additional data about perinatal outcomes. This will be the aim of our next project. Second, we did not wait all the pregnancies to end with the aim to share our data without loosing time.

4.2. Conclusion and recommendations

Even though we found out that COVID-19infection had similar clinical characteristics and a similar rate of pneumonia in pregnant women, the data obtained was based on a limited sample size and a definitive conclusion on weather the disease is worse or not in pregnant women could not be stated strictly. Metaanalysis for more reliable conclusions are needed in the field.

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Author Contribution

Concept: OS, KK, BK; Design: KK, YA, RD; Control: BK, RD, ADA; Data collection: KK, YA, OS; Analysis: ADA, AÖ, BK; Literatüre review: RD, BK; Writing: AÖ, KK; Critical review: OS, BK, ADA.

Conflict of İnterest

There is no conflict of interest between the authors

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